Synthesis and Insecticidal Activity of Novel *N*-Oxalyl-*N*-methylcarbamates

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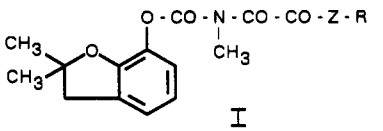
A series of novel 2,3-dihydro-2,2-dimethyl-7-benzofuranyl *N*-oxalyl-*N*-methylcarbamate insecticides (*N*-oxalyl derivatives of carbofuran) containing carboxylic acid or carboxylate substituent were prepared. *N*-Oxalyl derivatives of carbofuran were examined for toxicity to white mice and a wide variety of economically important pests and for systemic activity in plants. Compared to the parent insecticide, carbofuran, the derivatives displayed significantly reduced toxicity to the white mouse. Two of the derivatives [oxamic acid, carboxymethyl-, (2,3-dihydro-2,2-dimethyl-7-benzofuranyl) ester, ester with methyl salicylate, compound 1; and oxamic acid, carboxymethyl-, (2,3-dihydro-2,2-dimethyl-7-benzofuranyl) ester, ester with methyl *p*-hydroxybenzoate, compound 8] showed 700–1000 times less toxicity to the mouse than the nonderivatized carbofuran on a weight basis. All of the derivatives were highly effective insecticides against a wide variety of insects. The derivatives also displayed a wide spectrum of systemic pesticide activity comparable or superior to carbofuran in the cut stem, soil, and foliar applications.

INTRODUCTION

The derivatization of known insecticides to produce novel proinsecticidal compounds that exhibit improved properties such as greater residual effectiveness and lower mammalian toxicity and still retain their insecticidal activity continues to provide new and useful insecticides. Efforts with carbamate insecticides in particular have yielded a variety of new insecticidal compounds that are safer to mammals (Black et al., 1973; Drabek, 1983; Fahmy and Fukuto, 1981; Fahmy et al., 1978; Heywang et al., 1983; Kaplan, 1980).

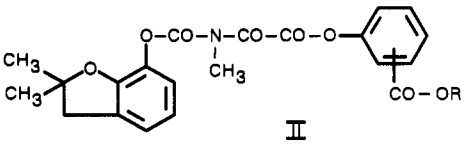
Synthesis by incorporation of the functional groups from systemically active molecules into derivatized carbamates resulting in compounds which possibly may have unusual increased plant systemic activity is considered one of the classical approaches. Crisp (1972) reported that for an insecticide to be phloem mobile a *–COOH* functional group would be necessary. The author also proposed that the carboxyl moiety must be labile within the plant, however, since ionizable carboxyl groups decrease insecticidal activity. Therefore, the authors concluded that the best structure–activity relationship would be obtained by developing an insecticide with an acidic group that would be metabolized *in vivo* to yield the parent compound as a product of the reaction after the plasmalemma has been permeated. The authors proved that malonyl-trichlorfon and succinyl-trichlorfon, when applied to the primary leaves or cotyledons of soybean plants, translocated to the terminal growth. Further, a carboxylic acid moiety when attached to the hydroxyl group of trichlorfon apparently enhanced long-distance symplastic translocation. Rao et al. (1986) reported that pesticidal water-soluble amino acid sulfenylated carbamates were useful as broad spectrum insecticides and miticides, particularly as systemic insecticides. Price (1979) reported that phosphoric, sulfonic, and carboxylic acid groups all contribute to phloem transport. The useful functional groups having a free carboxylate moiety are benzoates, acetates, amino acids, phenylacetates, phenoxyacetates, indoleacetates, nicotinic acid esters, sugars, etc. These functional groups are inherent in numerous molecules that translocate in the phloem of plants, e.g., amino acids, plant hormones, and numerous herbicides. The rationale has therefore been to design derivatives of conventional carbamate insecticides having physical properties that may result in their translocation throughout a treated plant after application to either foliage or roots. Such derivatives should also be susceptible to biological modification so as to be converted to the original parent carbamate insecticide.

This paper is concerned with the synthesis and insecticidal evaluation of certain novel 2,3-dihydro-2,2-dimethyl-7-benzofuranyl *N*-oxalyl-*N*-methylcarbamates of formula **I** (*N*-oxalyl derivatives of carbofuran) (Mallipudi



I

and Hollingshaus, 1986), where Z is O, N, or S and R is a variety of different substituents. The preferred compounds are those of formula **II**, where R is H, C_1–C_4 alkyl,



II

benzyl, and salts of the acid. The novel carbamates of formula **II** in which the *COOR* group is at the ortho, meta, or para position and represents a carboxylic acid function, a carboxylate salt function, or a carboxylic ester function have been found to be highly effective insecticides, which possess systemic insecticidal activity and exhibit greatly reduced mammalian toxicity compared to carbofuran, the carbamate insecticide from which they are derived. Compounds of formula **I** have received some attention in the patent literature (Heywang et al., 1983). In particular,

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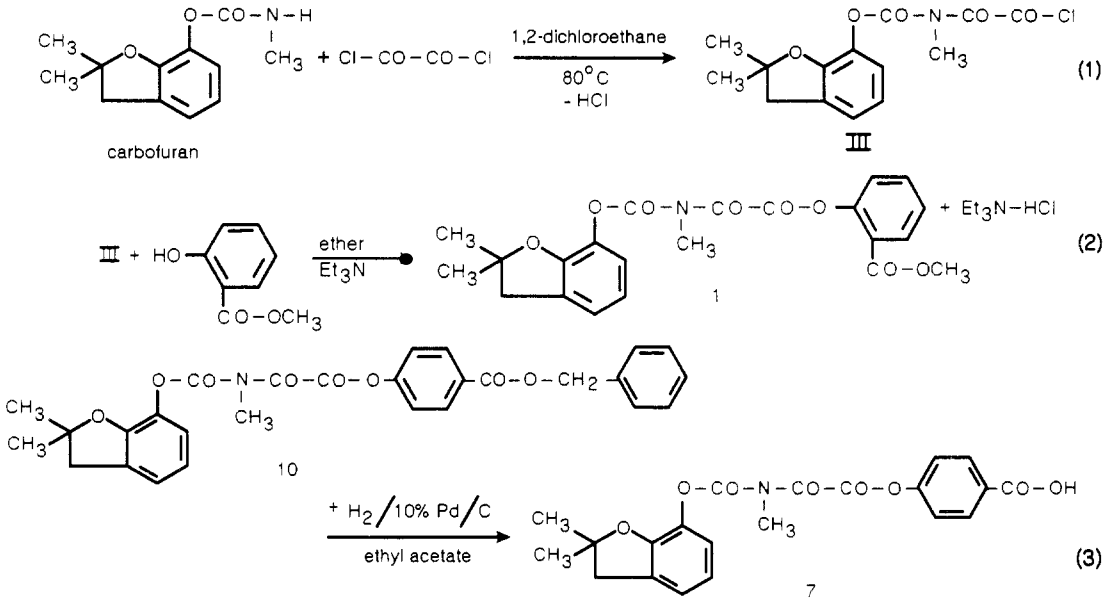
Scheme 1



this patent covered compounds in which R represents alkyl, alkynyl, aryl, halogen, etc. However, substituents with carboxylate functional groups (formula **II**) have not been disclosed.

MATERIALS AND METHODS

Technical grade carbofuran obtained from a commercial source (FMC Corp., Princeton, NJ) was used as starting material after purification by recrystallization from appropriate solvents (ether, hexane, dichloromethane).

Synthesis of Carbamic Acid, (Chloroglyoxyloyl)methyl-, 2,3-Dihydro-2,2-dimethyl-7-benzofuranyl Ester (III). The synthesis of intermediate formula **III** was accomplished by reacting carbofuran with oxalyl chloride according to the method of Heywang et al. (1983) as shown in eq 1 of Scheme 1.

Oxalyl chloride (1.5 g, 0.012 mol) was added dropwise to a stirred solution of carbofuran (2.2 g, 0.01 mol) in 30 mL of 1,2-dichloroethane. Upon completion of the addition, the reaction mixture was warmed slowly to 80 °C and maintained at this temperature until no more hydrogen chloride was evolved. The reaction mixture was cooled to room temperature and the solvent removed by distillation under reduced pressure to yield a viscous oil. The crude viscous oil was later solidified at room temperature, and thus the desired intermediate formula **III** was obtained with quantitative yield.

Synthesis of Oxamic Acid, Carboxymethyl-, (2,3-Dihydro-2,2-dimethyl-7-benzofuranyl) Ester, Ester with Methyl Salicylate (Compound 1). Compound **1** was synthesized by the reaction between intermediate formula **III** and methyl salicylate in triethylamine as shown in eq 2 of Scheme 1.

Intermediate formula **III** (3.1 g, 0.01 mol) was dissolved in anhydrous diethyl ether (20 mL), and methyl salicylate (1.5 g, 0.01 mol) was added dropwise to the stirred solution followed by the dropwise addition of triethylamine (1.5 g, 0.015 mol). Upon completion of the addition, the reaction mixture was allowed to stir at room temperature for 3 h and filtered, and the organic filtrate was washed with water. The organic phase was separated, dried over anhydrous magnesium sulfate, and filtered and the solvent removed under reduced pressure. The oily residue was treated with an ether–hexane mixture and the resulting white solid filtered off and dried to give compound **1**, mp 128–129 °C. The proton nuclear magnetic resonance (P NMR) spectrum showed the following absorption (chloroform-*d* TMS): The downfield shift and singlet for NCH_3, which for carbofuran occurred as a broad doublet at δ 2.9, were consistent with substitution of the proton of the carbamoyl moiety. Utilizing the above procedure and substituting the appropriate *o*-, *m*-, or *p*-hydroxybenzoate ester for the methyl salicylate, amines, and thiols, compounds **2–30** listed in Table 1 were prepared.

Synthesis of Oxamic Acid, Carboxymethyl-, (2,3-Dihydro-2,2-dimethyl-7-benzofuranyl) Ester, Ester with *p*-Hydroxybenzoic Acid (Compound 7) (Eq 3 of Scheme 1). The oxamic acid, carboxymethyl-, (2,3-dihydro-2,2-dimethyl-7-benzofuranyl ester, ester with benzyl *p*-hydroxybenzoate (compound **10**; 1.5 g) dissolved in 20 mL of ethyl acetate was added to 20 mL of ethyl acetate containing a catalytic amount (0.33 g) of 10% palladium on carbon. The resulting mixture was stirred and hydrogen gas (120 mL) introduced over a 2.5-h period at room temperature. Upon completion of the hydrogen addition, the reaction mixture was filtered to remove solids and the organic filtrate concentrated under reduced pressure to yield 1.9 g (93% yield) of the desired compound **7** with mp 165–166 °C. In a similar manner, compound **4** listed in Table 1 was prepared from compound **6**.

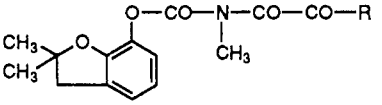
Preparation of Salts. An acetone solution containing about 1 M equiv of an amine or quaternary ammonium hydroxide was added to an acetone solution containing the appropriate benzoic acid isomer. The mixture was stirred to ensure salt formation. A portion of the resulting solution was evaporated to dryness and the residue identified by its infrared spectral properties. Utilizing this procedure yielded compounds **31–42** listed in Table 2.

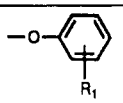
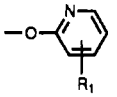
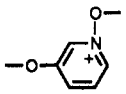
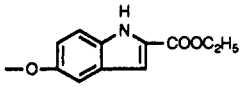
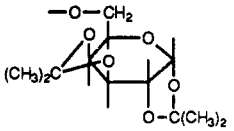
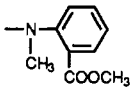
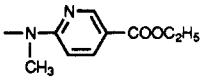
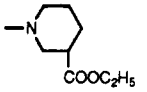
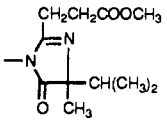
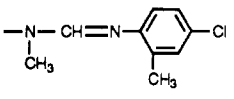
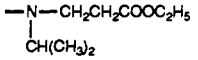
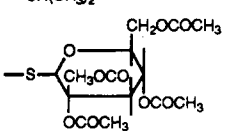
Products were purified by crystallization from solvents hexane and hexane–ether. Liquid or oily products were purified by column chromatography on silica gel eluting with ether–hexane (1:1). P NMR spectra were recorded with a Varian T-60A NMR spectrometer (chloroform-*d* TMS), and infrared spectra were recorded on a Perkin-Elmer Model 137 B infrared spectrophotometer using Nujol mulls or neat film. Melting points and elemental analyses for the individual compounds **1–30** are presented in Table 1.

Insecticidal Activity. The insecticidial activity of *N*-oxalyl derivatives of carbofuran was tested against various species of economically important insects. All tests were performed at 27 °C. Any test showing greater than 50% mortality was repeated at progressively lower concentrations (usually 10× dilution) until no further activity was observed. The bioassays were designed to provide a rapid estimate of insecticidal activity. In the 0–9 mortality rating scale (Table 3), for example, 0, 8, and 9 represent no kill, 86–99% kill, and 100% kill, respectively. The rating scale 9 represents the highest toxicity rating. The absence of a number indicates that no test has been run at that particular dosage. The insecticidal activity of the compounds against a variety of insects (Table 3) at various concentrations of active ingredient in acetone–water solutions was determined by the following insecticidal test examples.

Test I. Tobacco Budworm (Heliothis virescens) Eggs. A young cotton leaf about 7–8 cm long was dipped in a test suspension with agitation for 3 s. Eggs were collected on cheesecloth and cut into 10–20-mm squares containing about 50–100 eggs (6–30

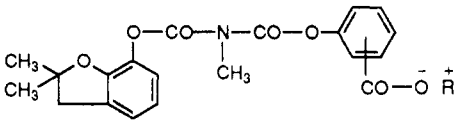
Table 1. Physical Properties and Elemental Analyses of *N*-Oxalyl Derivatives of Carbofuran



R	R_1	compd	mol wt	mp, °C	analysis					
					calcd			found		
					C	H	N	C	H	N
	*o*-$COOCH_3$	1	427.44	128–129	61.81	4.96	3.28	61.29	5.25	3.51
	o-$COOC_2H_5$	2	441.47	low mp	62.57	5.26	3.17	62.81	5.75	3.33
	o-$COOCH_2$-C_6H_5	3	503.54	132–135	66.78	5.01	2.78	66.62	5.24	2.79
	m-COOH	4	413.41	165–170	61.01	4.64	3.39	61.05	4.87	3.07
	m-$COOCH_3$	5	427.44	oil	61.81	4.96	3.28	60.40	5.26	3.15
	m-$COOCH_2$-C_6H_5	6	503.54	oil	66.78	5.01	2.78	67.31	5.16	2.51
	p-COOH	7	413.41	165–166	61.01	4.64	3.39	60.84	4.98	3.35
	p-$COOCH_3$	8	427.44	146–148	1.81	4.96	3.28	60.99	5.16	3.34
	p-$COOC_4H_9n$	9	461.53	86–90	63.95	5.81	2.98	64.25	5.87	3.31
	p-$COOCH_2$-C_6H_5	10	503.54	84–85	66.18	5.01	2.78	66.52	5.30	2.75
	p-CH_2COOH	11	427.44	143–147	61.81	4.96	3.28	61.98	5.30	3.10
	p-CH_2COOCH_3	12	441.47	viscous	62.57	5.26	3.17	62.88	5.75	2.87
	p-CH_2COOCH_2-C_6H_5	13	517.57	87–89	67.29	5.27	2.71	67.04	5.58	2.61
	p-OCH_2COOH	14	443.44	136–131	57.58	4.78	3.16	59.15	5.08	3.14
	p-OCH_2COOCH_2-C_6H_5	15	533.51	viscous	65.28	5.11	2.63	64.68	5.64	2.55
-OCH_2COOR_1	H	16	351.34	viscous	54.69	4.89	3.99	54.44	5.21	3.49
	C_2H_5	17	379.40	viscous	56.98	5.59	3.69	57.07	5.53	3.75
	CH_2-C_6H_5	18	441.47	viscous	62.57	5.26	3.17	61.17	5.69	2.92
	H	19	370.39	141–144	61.61	4.91	7.57	61.71	4.95	7.50
	o-$COOCH_3$	20	428.40	130–133	58.87	4.72	6.54	58.98	4.89	6.36
		21	386.39	125–128	59.06	4.71	7.25	58.66	5.15	7.24
		22	480.51	64–68	62.49	5.05	5.83	62.60	5.78	5.66
		23	535.6	low mp	58.30	6.22	2.62	58.38	6.51	6.63
		24	440.49	113–115	62.70	5.50	6.40	63.40	5.47	6.39
		25	455.51	123–125	60.64	5.54	9.23	60.25	5.78	9.16
		26	432.52	low mp	61.09	6.54	6.48	61.10	6.65	6.32
		27	501.59	109–113	59.86	6.24	8.38	60.03	6.42	8.14
		28	457.95	viscous	60.32	5.29	9.18	59.79	5.30	8.95
		29	434.00	viscous	60.80	6.97	6.50	59.77	6.48	6.20
		30	639.68	53–56	52.57	5.21	2.19	53.25	6.00	2.50

h old). A square of cheesecloth with eggs was also dipped similarly in the test suspension and placed on the treated leaf. The combination was placed in the hood to dry. Following this, the combination was placed in an 8-oz Dixie cup (240 mL, 6 cm tall, 9.5-cm top diameter, 8-cm bottom diameter), containing a 5-cm length of damp dental wick. A clear plastic lid was put on the top of the cup, and the treatments were held for 3 days before mortality counts were made.

Table 2. Ammonium Salts of (2,3-Dihydro-2,2-dimethyl-7-benzofuranyl)carboxymethyloxamate Benzoic Acids



compd	positional isomer	R	
31	*m*	$^{\bullet}(CH_3)_2CH\text{-}NH_2$	isopropylammonium
32	*m*	$^{\bullet}n\text{-}C_{18}H_{37}\text{—}N(CH_2CH_2O)_x(CH_2CH_2O)_y$	dipolyethoxylated octadecylammonium
33	*m*	$^{\bullet}C_6H_5CH_2\text{—}N^{+}(CH_3)_3\ ^{\bullet}OH^{-}$	benzyltrimethylammonium
34	*m*	$^{\bullet}(C_2H_5)_3N$	triethylammonium
35	*m*	$^{\bullet}C_6H_5(CH_2)_4\text{—}NH_2$	4-phenylbutylammonium
36	*m*	$^{\bullet}(C_6H_{11})_2NH$	dicyclohexylammonium
37	*p*	$^{\bullet}(CH_3)_2CH\text{-}NH_2$	isopropylammonium
38	*p*	$^{\bullet}n\text{-}C_{18}H_{37}\text{—}N(CH_2CH_2O)_x(CH_2CH_2O)_y$	dipolyethoxylated octadecylammonium
39	*p*	$^{\bullet}C_6H_5CH_2\text{—}N^{+}(CH_3)_3\ ^{\bullet}OH^{-}$	benzyltrimethylammonium
40	*p*	$^{\bullet}(C_2H_5)_3N$	triethylammonium
41	*p*	$^{\bullet}C_6H_5(CH_2)_4\text{—}NH_2$	4-phenylbutylammonium
42	*p*	$^{\bullet}(C_6H_{11})_2NH$	dicyclohexylammonium

Table 3. Insecticidal Activity of *N*-Oxalyl Derivatives of Carbofuran against Economically Important Pests[a]

	TBW[b] eggs, ppm			bean aphid, ppm			SAW,[c] ppm				SCR,[d] kg/ha			malaria mosquito larvae, ppm			mosquito adult, ppm		lygus bug, ppm		leafhopper, ppm			TBW, ppm			SAW cut stem systemic, ppm			German cockroach residual, ppm	
compd	300	100	10	100	10	1	1000	100	10	7d	50	10	1	1.2	0.4	0.04	10	1	100	10	100	10	1	1000	100	1	100	10	1	1000	100
carbofuran	9	0	–[e]	9	9	8	9	9	5	7	9	9	9	9	9	0	9	2	9	3	9	9	0	9	7	0	9	9	0	9	0
1	9	9	8	9	7	7	9	9	0	9	9	9	9	8	8	0	9	3	9	6	9	9	0	9	0	–	9	8	3	0	–
2	9	9	8	7	0	–	9	9	0	9	9	9	7	8	8	0	9	0	0	–	9	0	–	9	0	–	9	8	0	0	–
4	9	8	0	9	8	0	9	9	0	0	9	9	8	9	9	0	9	9	–	0	9	3	–	8	0	–	9	0	–	0	–
5	9	9	3	9	9	4	9	9	0	9	9	9	8	9	9	0	9	3	9	5	9	6	–	9	0	–	9	0	–	0	–
7	9	9	8	9	9	8	9	9	0	6	9	9	6	9	9	6	9	6	–	–	9	5	0	9	4	0	9	9	3	2	0
8	9	8	0	9	7	0	9	9	0	9	9	7	0	8	8	0	9	0	9	0	9	9	0	9	0	–	9	7	–	0	–
9	9	9	8	7	0	0	9	9	0	9	9	9	9	8	5	0	9	0	9	0	9	0	–	9	0	–	9	0	0	0	–
10	9	9	8	9	7	7	9	9	0	6	9	9	5	9	9	0	9	0	–	–	9	0	–	7	0	–	3	0	0	0	–
16	9	9	0	9	9	6	9	9	6	2	9	9	9	9	9	3	9	9	–	–	9	7	–	9	6	0	9	9	0	0	–
22	9	8	7	9	9	0	9	9	0	9	9	9	7	9	4	0	9	4	–	–	9	0	0	8	0	0	9	9	0	0	–
23	9	7	0	9	4	0	9	9	0	9	9	–	–	8	6	0	9	4	8	5	9	9	0	9	0	–	9	9	–	0	–
24	8	5	0	0	–	–	9	9	0	7	9	9	4	0	–	–	9	3	9	3	9	8	–	7	3	–	9	0	–	0	–
36	–	9	5	9	8	3	–	9	0	0	9	9	7	9	8	0	9	7	–	–	9	9	0	9	0	0	9	0	0	9	6
37	–	9	5	9	9	0	–	8	0	0	9	9	9	9	6	0	9	5	–	–	9	9	0	7	0	0	9	0	0	9	0

[a] Mortality rating system: 0 = no kill; 1 = 10–25% kill; 2 = 26–35% kill; 3 = 36–45% kill; 4 = 46–55% kill; 5 = 56–65% kill; 6 = 66–75% kill; 7 = 76–85% kill; 8 = 86–99% kill; 9 = 100% kill. [b] Tobacco budworm. [c] Southern armyworm. [d] Southern corn rootworm. [e] –, no test run at that particular dosage.

Test II. Bean Aphid (Aphis fabae) Mixed Instar. Pots containing single nasturtium plants (*Tropaeolum* sp.) about 5 cm tall were infested with about 100–200 aphids 1 day before the test. Each pot was sprayed with the test formulation for two revolutions of a 4 rpm turntable in a hood, using an atomizer. The spray tip was held about 15 cm from the plant and the spray directed so as to give complete coverage of the plants and the aphids. The sprayed pots were set on their sides on white enamel trays and held for 2 days, following which time mortality estimates were made.

Test III. Southern Armyworm (Spodoptera eridania) Third Instar Larvae. The leaves of a Sievae lima bean plant expanded to 7–8 cm in length were dipped in a test suspension with agitation for 3 s and placed in a hood to dry. A leaf was then excised and placed in a 100 × 10 mm Petri dish containing a damp filter paper on the bottom and 10 third-instar larvae. The dish was maintained for 5 days before observations were made of mortality, reduced feeding, or any interference with normal moulting.

Test IV. Southern Armyworm (S. eridania) 7-Day Residual Activity. The plants treated in test III were maintained under high-intensity lamps in the greenhouse for 7 days. These lamps duplicate the effects of a bright sunny day and were kept on for a 14-h day length. After 7 days, the foliage was sampled and assayed as in test III.

Test V. Southern Corn Rootworm (Diabrotica undecimpunctata howardi) Third Instar Larvae. One cubic centimeter of fine talc was placed in a 30-mL wide-mouth screw-top glass jar. One milliliter of the appropriate acetone suspension was

pipetted onto the talc so as to provide 1.25, 0.25, and 0.025 mg of active ingredient per jar. The jars were set under a gentle air flow until the acetone was evaporated. The dried talc was loosened, 1 cm^3 of millet seed was added to serve as food for the insects, and 25 mL of moist soil was added to each jar. The jar was capped, and the contents were thoroughly mixed on a Vortex mixer. Following this, 10 third-instar rootworms were added to each jar and the jars loosely capped to allow air exchange for the larvae. The treatments were held for 6 days before mortality counts were made. Missing larvae were presumed dead, since they decomposed rapidly and could not be found. The concentrations used in this test correspond approximately to 50, 10, and 1 kg/ha, respectively.

Test VI. Common Malaria Mosquito (Anopheles quadrimaculatus) First Instar Larvae. Concentrations of 1.2, 0.4, and 0.04 ppm were obtained by pipetting 1 mL of 300, 100, and 10 ppm acetone solutions or suspensions of the compound into a 400-mL beaker containing 250 mL of deionized water. The contents were stirred with the pipet as the 1 mL was added. A wax paper ring about 1 cm wide was floated on the surface of the water to keep the eggs from floating up the meniscus curve and drying out on the side of the beaker. A spoon made from screen was used to transfer about 100 eggs (6–30 h old) into the test beaker. The beakers were held for 2 days, following which time observations of kill of newly emerged larvae or delayed hatch were recorded.

Test VII. Common Malaria Mosquito (A. quadrimaculatus) Adults. Acetone test suspensions were poured into 60-mL wide-mouth jars each containing a microscope slide. The slides were removed from the test suspensions with clean forceps and placed to dry horizontally on the mouths of 120-mL wide-mouth jars. When dry, they were put into the same 120-mL jars. Ten 4–5-day-old adult mosquitoes of mixed sexes were placed in each jar with the treated microscope slide. A piece of cheesecloth held on by an elastic band served as a lid for the jar. A wad of cotton soaked in 10% honey solution was placed on the lid as a food supply for the mosquitoes. Treatments were held for 1 day before mortality counts were made.

Test VIII. Tarnished Plant Bug (Lygus lineolaris) Adults. About 5 cm long primary leaves of Sieva lima beans were dipped into the test formulation for 3 s with agitation and placed in the hood to dry. The leaf was then placed in an 8-oz Dixie cup (2168-ST, 240 mL, 6 cm high, 9.5-cm top diameter, 8-cm bottom diameter) into which a 5-cm length of damp dental wick had been previously placed. Insects were aspirated out of the colony and 10 insects placed in each cup. Treatments were held for 3 days, following which time mortality counts were made.

Test IX. Western Potato Leafhopper (Empoasca abrupta) Adults. A Sieva lima bean leaf about 5 cm long was dipped into the test formulation for 3 s with agitation and placed in a hood to dry. The leaf was placed in a 100 × 10 mm Petri dish containing a moist filter paper on the bottom. About 10 adult leafhoppers were added to each dish, and the treatments were kept for 3 days before mortality counts were made.

Test X. Tobacco Budworm (H. virescens) Third Instar Larvae. Cotton cotyledons were dipped into the test formulation and allowed to dry in a hood. When dry, each cotyledon was cut into quarters and 10 sections were placed individually in 30-mL plastic medicine cups containing a 5–7 mm long piece of damp dental wick. One third instar larva was added to each cup and a cardboard lid placed on the cup. Treatments were maintained for 3 days before mortality counts and estimates of reduction in feeding damage were made.

Test XI. Cut Stem Systemic Uptake: Southern Armyworm (S. eridania) Third Instar Larvae. The mortality of insects from the cut stem systemic uptake tests was assessed as follows: The test compound was formulated as an emulsion containing 0.1 g of the test compound, 0.1 g of a polyoxyethylated vegetable oil in 0.4 g of water, 10 mL of acetone, and 90 mL of water. This was diluted 10-fold with water to give the 100 ppm emulsion for the test. Subsequent 10-fold dilutions were made with water as needed to provide 10 and 1 ppm test emulsions. Sieva lima bean plants with just the primary leaves expanded were used in this test. They were cut off at least 2.5 cm above the soil level to avoid contamination with soil bacteria that will cause decay of the stem during the test. Sixty-milliliter bottles containing 50 mL of the test emulsion at 100 ppm initially each have one Sieva lima bean stem inserted into the emulsion. The stem was wrapped with a bit of cotton to hold the end off the bottom of the bottle and to limit evaporation and volatilization of the compound. The test bottles were held for 3 days at 27 °C to enable the compound to be taken up into the leaf, keeping the room fluorescent lights on for 24 h/day. A leaf was removed from the plant after 3 days and placed in a Petri dish with 10 southern armyworms as described for test III. The Petri dishes were held for 3 days before mortality counts and notations of feeding damage were taken.

Test XII. Root (Xylem) and Foliar (Phloem) Systemic Uptake. A more basic aspect of this novel analog synthesis was investigation of the translocation properties of these compounds in the plant. Two primary screens for systemic insecticidal activity were established. The first screen for plant systemic insecticidal activity involved the application of solutions of test compounds to the soil of pots of Sieva lima bean plants or the water of pots of flooded rice plants. A standard screening rate of 10 kg/ha was used with follow-up testing at 1.0 and 0.1 kg/ha. Systemic activity was determined via bioassays of foliage at variou time intervals after treatment. Test insects were either caged on the foliage of plants or in Petri dishes with excised leaves. Insects used in bioassay were southern armyworm (*S. eridania*), tarnished plant bug (*L. lineolaris*), and western potato leafhopper (*E. abrupta*).

A second screen for systemic activity involved foliar application of the test compounds. This test involved dipping the primary leaves of Sieva lima bean plants or the first three leaves of cotton plants into 1000 ppm solutions of test compounds followed by bioassay of new growth at 7 days after treatment. Southern armyworm was used in this bioassay, and the procedure was followed was as described for test III.

Test XIII. German Cockroach (Blatella germanica) Adult Male, Residue Test. One milliliter of a 1000 ppm acetone solution of the test material was pipetted slowly over the bottom of a 150 × 15 mm Petri dish so as to give as uniform coverage as possible. After the deposit has dried, 10 adult male cockroaches were placed in each dish and the lid was added. Mortality counts were made after 3 days.

Toxicity in Mice. Mouse toxicity was determined orally on 4-month-old female Swiss white mice (25–30 g) using corn oil as the carrier according to the usual procedure (Hollingworth et al., 1967). The test compounds were dissolved in corn oil, and 100 μL was introduced orally by means of a syringe equipped with a small animal feeding probe. Mortality was evaluated 48 h after the treatment. The average percentage mortality of the replicates within each dose was plotted on a logarithm–probit paper, and the LD_{50} (dosage required to kill 50% of the test population) was obtained.

RESULTS

Insecticidal Activity of *N*-Oxalyl Derivatives of Carbofuran against Economically Important Pests. Screening data for a representative number of *N*-oxalyl derivatives of carbofuran against a variety of economically important pests are presented in Table 3. The results showed that *N*-oxalyl derivatives of carbofuran were exceedingly effective insecticides with variable toxicity to a number of insects tested. In many cases, these compounds were more toxic to insects than carbofuran on a molar basis. Although no obvious relationship between structure and insecticidal activity was evident, activity appeared to be strongly associated with the novel carbamates of formula **II** in which the *COOR* group was in the ortho, meta, or para position and represented a carboxylic acid function (compounds **4** and **7**), a carboxylate salt function (compounds **36** and **37**), and a carboxylic ester function (compounds **1**, **2**, **5**, **8**, and **9**).

The *N*-oxalyl derivatives of carbofuran were more effective than carbofuran against tobacco budworm eggs. The derivatives were active at 10 ppm against tobacco budworm eggs, whereas carbofuran did not show any

Table 4. Systemic Activity of *N*-Oxalyl Derivatives of Carbofuran in Lima Beams after Soil Drench Application

	% mortality at 3 days after treatment							
	southern armyworm, kg/ha				leafhopper, kg/ha			
compd	10	4.7	2.2	1.0	10	4.7	2.2	1.0
carbofuran	100	93	70	30	100	100	86	86
1	95[a]	68	20	30	100	100	100	90
5	100	83	3	–[b]	100	100	50	–
8	93	63	14	0	100	80	60	0
23	80	46	3	0	100	100	30	20
30	77	17	0	–	100	100	0	–

[a] 100% mortality of southern armyworm was observed at 10 days after treatment when first trifoliate was assayed. [b] The absence of a number indicates that no test has been run at that particular dose.

Table 5. Root (Xylem) Systemic Uptake: Control of Rice Pests after Water Drench Application of *N*-Oxalyl Derivatives of Carbofuran at 10 kg/ha

	% mortality at days indicated after infestation								
	southern armyworm			lygus bug			leafhopper		
compd	1	2	3	1	2	3	1	2	3
control	0	0	0	0	0	0	0	0	0
carbofuran	100	–[a]	–	80	100	–	90	100	–
1	40	100	–	100	–	–	90	100	–
23	10	70	90	80	100	–	100	–	–

[a] The absence of a number indicates that no test has been run at that particular dose.

activity at 100 ppm and mortality of eggs was observed only at 300 ppm. However, the derivatives were less active than carbofuran against tobacco budworm third instar larvae at the 100 ppm level (Table 3).

For the piercing–sucking insects, many of the *N*-oxalyl derivatives showed contact toxicity as high as that of carbofuran against bean aphid and leafhoppers. The effective concentration was as low as 1 ppm for the bean aphid and 10 ppm for leafhopper. Compared to carbofuran, the *N*-oxalyl derivatives showed equal or higher insecticidal activity against the southern armyworm, southern corn rootworm, malaria mosquito larvae, and mosquito adult. With the exception of a few derivatives (e.g., compounds **1**, **5**, **23**, and **24**), the *N*-oxalyl derivatives of carbofuran were generally less active (or totally inactive) at all concentrations used than the parent carbamate in controlling the lygus bug.

A number of derivatives, as shown in Table 3, showed considerably high activity in their cut stem systemic action in plants against southern armyworm. Most of the *N*-oxalyl derivatives of carbofuran tested were highly active via soil drench application against southern armyworm and leafhopper (Table 4). Compound **1** showed considerable systemic activity at 1 kg/ha, which was the lowest concentration tested. Also, compound **1** exhibited excellent root uptake and controlled southern armyworm even at 10 days after treatment. Compounds **1** and **23** were also active in water drench test with rice against southern armyworm, lygus bug, and leafhopper (Table 5). Compound **1** showed systemic activity via foliar application on cotton against tobacco budworm (Table 6). In tests for systemic activity, compound **1** or other derivatives were comparable or slightly superior to carbofuran.

In contrast, these *N*-oxalyl derivatives, except compounds **36** and **37**, were totally inactive as residual insecticide against German cockroaches. Carbofuran showed 100% control (rating scale 9) against cockroaches at a 1000 ppm dosage. Compared to total inactivity of benzoic acid isomers (compounds **4** and **7**), their corresponding amine salts (compounds **36** and **37**) were the only compounds showing activity against cockroaches equal to or higher than that of carbofuran. On the basis of the toxicity data, no apparent conclusions can be drawn for the lack of the derivatives toxicity to cockroaches.

Table 6. Foliar (Phloem) Systemic Uptake: Control of Tobacco Budworm on Cotton and Southern Armyworm on Lima Beans after Foliar Application of Carbofuran and Compound 1 at 1000 ppm

	% mortality[a]			
	cotton[b]		lima beans[c]	
compd	4th leaf	5th leaf	primary leaf	1st trifoliolate
control	0	0	0	0
carbofuran	77	43	100	6
1	70	20	100	0

[a] Leaves were bioassayed 7 days after treatment. [b] Compounds applied to first three leaves. [c] Compounds applied to primary leaves.

Table 7. Toxicity of Certain Novel *N*-Oxalyl Derivatives of Carbofuran to Mice

		acute mouse (oral) LD_{50}		selective
compd	mol wt	mg/kg	mmol/kg	toxicity ratio[a]
carbofuran	221.3	2[b]	9	
1	427	1403	3286	365.1
4	413.4	38	92	10.2
5	427	96	225	25.0
7	413.4	44	106	11.8
8	427	>2000	>4684	>520.4

[a] LD_{50} of carbofuran derivative in mmol/kg divided by LD_{50} of carbofuran in mmol/kg. [b] LD_{50} value of carbofuran from Black et al. (1973).

Toxicity to Mice. The mice toxicity of the *N*-oxalyl derivatives of carbofuran is presented in Table 7. To account for the differences in molecular weights of the compounds, toxicity data are expressed on a molar basis as well as on a weight basis; i.e., LD_{50} is given in terms of millimoles per kilogram. The various *N*-oxalyl derivatives of carbofuran were substantially less toxic to mice compared to carbofuran. In general, the data were similar to those reported previously for the derivatized methylcarbamates (Black et al., 1973; Fahmy et al., 1978; Fahmy and Fukuto, 1981). For example, on a weight basis compounds **1** and **8** were more than 700- and 1000-fold less toxic than carbofuran. This is the first case in which a substantial reduction in mice toxicity was achieved with a carbofuran derivative that retained good insecticidal activity. Of interest is the low mammalian toxicity of compound **8** compared to that of compound **7**, i.e., >2000 mg/kg compared to 44 mg/kg, respectively. These two compounds are a methyl ester and its corresponding acid analog, respectively. This comparison points out that it is possible that the benzoic acid ester analogs are more stable to acid-catalyzed hydrolysis compared to the benzoic acid analog.

DISCUSSION

Previous studies from various laboratories have shown that substitution of the hydrogen atom on the carbamoyl nitrogen of insecticidal methylcarbamate esters by different functional groups such as acyl (Fraser et al., 1967), dialkoxyphosphinothioyl (Fahmy et al., 1970), alkyl- and arylsulfenyl (Black et al., 1973), aminosulfenyl (Fukuto et al., 1975), symmetrical and asymmetrical *N,N'*-thiobis(carbamate)s (Fahmy et al., 1974, 1978), and *N*-sulfinyl (Fahmy and Fukuto, 1981) almost always produced compounds of lower mammalian toxicity compared to the parent methylcarbamates. Derivatization of insecticidal methylcarbamates also resulted in compounds of lower

anticholinesterase activity and with physical properties different from those of the parent methylcarbamates (Black et al., 1973; Fahmy and Fukuto, 1981). In many cases the derivatives were more effective than the parent compound against insects, even though each derivative has only about half the toxic carbamate on a weight basis. The improved or sustained insecticidal activity may be attributed to the improved lipophilicity of the derivatives compared to that of the parent methylcarbamate, resulting in compounds that penetrate faster into insects. The instability of these derivatives in biological systems of pests to release readily the toxic parent methylcarbamate accounts for the insecticidal activities observed for these compounds. The improved lipophilicity of the *N*-oxalyl derivatives might have played a role in faster penetration into tobacco budworm eggs, thus resulting in increased toxicity.

The lower mammalian toxicities of *N*-oxalyl derivatives of carbofuran are assumed to be due to the preferential metabolic detoxication of the derivatives to nontoxic products, a mechanism similar to that of other derivatized methylcarbamate esters (Black et al., 1973; Fahmy et al., 1978; Krieger et al., 1976; Miskus et al., 1969). In the target species, the active carbofuran is most likely generated *in vivo* from the *N*-oxalyl derivatives of carbofuran, resulting in intoxication.

Synthesis of methylcarbamate derivatives containing a carboxylate moiety may result in compounds that possibly have unusual systemic activity. The rationale for the synthesis of these derivatives was based on the well-known fact that carboxylic acid groups are phloem mobile and may move downward as well as upward in plants (Price, 1979). Substitution of a carboxylic molecule to a methylcarbamate insecticide therefore may add or enhance phloem movement of the compound. The insecticide carbofuran has a slight phloem transport, and when a carboxylic ester is attached to the nitrogen of carbofuran, the phloem transport may increase. The esters may improve cuticular uptake. Once inside the plant, the ester may be hydrolyzed and the acid may lead into the phloem and move systemically in phloem.

Most of the *N*-oxalyl derivatives of carbofuran tested were highly active in foliar and in cut stem systemic uptake. The derivatives also were active against various insects when soil applied. A series of tests comparing carbofuran and compound 1 demonstrated that each of these compounds has systemic activity in foliar application on cotton. These findings suggest that the insect intoxication is consistent with the conversion of the derivative to the parent compound during the uptake intoxication process.

In conclusion, as in the case of different derivatized methylcarbamates mentioned in the literature, the various *N*-oxalyl derivatives of carbofuran described in this paper also showed extremely favorable properties of selectivity between insects and mice. The derivatives are more or equally as toxic as carbofuran in foliar and cut stem and root uptake tests against insects. Because of low mammalian toxicity, the derivatives could probably be used safely in the field by foliar application.

ACKNOWLEDGMENT

We thank Donald P. Wright, Jr., and Joel Fisher for the biological information incorporated into this paper.

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Received for review December 20, 1993. Accepted January 24, 1994.[⊗]

[⊗] Abstract published in *Advance ACS Abstracts*, March 1, 1994.